REMARKS

Status of the claims

Claims 37-75 are pending in this application.

Amendment to the Claims

Claims 1-36, 44-46, 48-51, 61-62, and 65 are cancelled without prejudice or disclaimer.

Claims 37-38, 40, 42, 47, 57, 63, 66, and 69 are amended. Claims 73-75 are added. Support for amended and newly added claims can be found althroughout in the specification and in the originally filed claims, as summarized in the table below.

Claim No.:	**Support in the Specification as Filed**
37	Paragraphs 32 (0.5×10^9 to 1×10^{10} heat inactivated *mycobacterium w*), support for this can also be found in Paragraph 85,85,93,105,108,113; paragraph 23 (primary and secondary (metastatic) cancers); paragraph 85 (multiple myeloma); paragraph 87 (breast cancer); paragraph 89 (esophageal cancer); paragraph 92 (bladder cancer); paragraph 101 (lung cancer); paragraph 107 (head and neck cancer); paragraph 113 (pancreas); and paragraphs 87 ,106 and 113 (metastatic carcinoma).
38	Paragraphs 21,87,88,91,93,98, 106, and 113 (symptomatic relief from pain, abnormal hemoglobin, cough, breathlessness, dysphagia, neutropenia or irregular sleep in the patient suffering from cancer).
40, 42, 47, 57	Corrected for typographical errors or to reflect corrected antecedent basis, no new matter was added.
63	Corrected for typographical errors or to reflect corrected antecedent basis, no new matter was added.
66	Paragraphs 32 (0.5×10^9 to 1×10^{10} heat inactivated *mycobacterium w*); paragraph 23 (primary and secondary (metastatic) cancers); paragraph 85 (multiple myeloma); paragraph 87 (breast cancer); paragraph 89 (esophageal cancer); paragraph 92 (bladder cancer); paragraph 101 (lung cancer);

	paragraph 107 (head and neck cancer); paragraph 113 (pancreas); and paragraphs 87, 106, and 113 (metastatic carcinoma)
69	Paragraph 21, corrected to more accurately reflect the claimed invention, no new matter was added.
73	Paragraph 85 (Intradermally);
74	Paragraph 93 (Superficial bladder cancer)
75	Paragraph 96 (Muscle invasive bladder cancer)

Claims 37-43, 47, 52-60, 63-64, 66-75 are currently under prosecution and after entry of the foregoing amendment remain subject to examination in this application. No new matter has been added by ways of the foregoing amendment, nor is any new issue of patentability raised. The claims as amended are submitted to place the application for allowance or in better form for appeal. Accordingly, entry and consideration of this amendment are respectfully requested.

Summary of Office Action

Claims 37-47 and 52-72 are rejected under 35 U.S.C. §112, First Paragraph, as allegedly being not enabled. Applicant traverses the rejection of claims 37-47 and 52-72.

Reconsideration of these rejections in view of the remarks set forth herein is respectfully requested.

Rejection of claims under 35 USC §112, lack of enablement

The final Action states a position of rejecting claims 37-47 and 52-72 for lack of being enabled. In rejecting these claims, positions 1-4 of the Action are:

POSITION 1: "[T]he instant specification . . . while reciting various preparations of *mycobacterium w* does not specify which of the types was actually utilized nor how much of composition was administered in the recited example."

POSITION 2: "[T]he required information, at the minimum, would be the actual composition administered to the patients, the dosage administered, the route of administration, and the frequency of administration."

POSITION 3: "[T]here in no method steps for the various solvent extractions recited . . . accordingly, it unclear which actual extract possesses any of the therapeutic properties; and

POSITION 4: "[C]ancer treatment is an extremely unpredictable art with a solid statistical data required to support it."

Responses to Positions

In response to POSITIONS (1), (3) and (4), without acquiescing to the asserted grounds of rejection and although Applicant disputes the interpretation of the art in the Action and solely in an effort to expedite prosecution of the pending claims to allowance Applicant has amended claims which moots the arguments stated in the Action. Independent claims 37 and 66 have been amended to limit the scope of claims to administering to a patient a pharmaceutical composition comprising about $0.5x10^9$ to 1×10^{10} units of heat inactivated *mycobacterium w.* Furthermore, the types of cancer have been limited to primary cancer or a secondary (metastatic) lesion thereof selected from one or more of multiple myeloma, breast cancer, esophageal cancer, bladder cancer, non small cell lung carcinoma, head and neck cancer, pancreatic cancer a cancer that metastasizes to bone, liver, or lung, or combinations thereof. Dependent claims 38-43, 47-60, 63-64, and 71-73, which depend on claim 1 incorporate all the limitations of claim 1. Likewise, dependent claims 68, and 70-72, incorporate all the limitations of claim 66. Independent claim 69 has been amended to limit the scope of claims to an effective amount of a pharmaceutical composition comprising heat inactivated *mycobacterium w.* Dependent claims 70-72, incorporate all the limitations of claim 69.

Applicant respectfully asserts that all requirements of 35 U.S.C. §112 are now met. Withdrawal of the rejection to the extent based on POSITION (1), (3), and (4) is respectfully requested.

With respect to POSITION (2), the current position stated in the Action appears to be that enablement requires Applicant to provide "[a]ctual composition administered to the patients, the dosage administered, the route of administration, and the frequency of administration." However, such is not the standard for enablement, and such a position lacks legal basis. Rather, it is well settled that "the scope of enablement must only bear a reasonable correlation to the

scope of claims". See *In re Fisher* 427 F.2d, 833, 839 111USPQ, 18, 24 (CCPA 1970) (*emphasis added*).

There are known techniques for treating a patient with cancer available to one skilled in the art that would not require undue experimentation[1]. As an example, WHO publication titled 'Cancer Pain Relief', published in 1996 provides guidelines to cancer pain relief, with opoid as an example. It provides *inter alia* that a drug could be administered through different routes and yet has same effect. For example on page 29, it is stated: "[T]he dose of morphine or other opoid is the same whether given subcutaneously, intramuscularly, or intravenously." Other routes of administration, such as "transdermal" or "spinal" are also considered to be routine. See page 29. On page 58 of the same report, it is stated that "[D]ecisions concerning the type of drug to be used [to treat or alleviate the pain related to cancer], the amount of the prescription, and the duration of therapy are best made by the medical professionals on the basis of the individual needs of each patient, and not by regulation". Therefore, techniques for treating or alleviating pain of a patient suffering with cancer are available to one skilled in the art and it would not require undue experimentation to carry out such treatments. Relevant portions of the WHO publication was previously provided in a response filed on December 17, 2010, in Appendix B and is again being provided for Office's convenience as Appendix B hereto. Entire document is available publicly on the WHO website (http://whqlibdoc.who.int/publications/9241544821.pdf).

The teachings of the specification and the known techniques provide for an enabling claim scope. For example, as explained in the previously filed response, the specification, *inter alia*, provides:

1. Examples of composition used in the specification demonstrating medical effect (as in Examples 4 to 9), is provided in Example 1a which consists of 0.5×10^9 heat killed whole cells of *mycobacterium w* in 0.1 ml. But the other disclosed compositions are also usable.

2. Examples of dose administered are:

- 0.1 ml as per example 4 to 8
- 0.2 ml initial dose as per example 8b, paragraph [0108]
- 0.3 ml as per Example 9

[1] Cancer therapies and their dosages, routes of administration and recommended usage are known in the art and have been described in such literature as the Physician's Desk Reference (PDR). Physicians' Desk Reference, 2002 (Hospital/Library Version) (ISBN 1563634112).

3. The route of administration in all examples of administration was intradermal, through intramuscular is also disclosed separately.

4. Examples of frequency of administration are:

Once a month

Example 5 of paragraph [0093], line 4,

Example 6 of paragraph [0097], line 4

Once every two weeks

Example 8(a) of paragraph [0105], line 7

Example 8(b) of paragraph [0108], line 6-8

Once a week

Example 8(a) of paragraph [0105], line 6

Example 4, Case 1, paragraph [0085], line 9 and case 3, paragraph [0089], line 11.

Biweekly

Example 9 of paragraph [0113], line 6.

In the Rule 1.132 Declaration, submitted in response to the previous Office Action, dated 2/18/2010, and incorporated herein by reference, the Declarant, Dr. B.R. Khamar, showed that several ongoing clinical trials are based on the teachings of the present invention and are being conducted following strict guidelines set for by regulatory authorities, such as FDA. Examples of ongoing clinical trials provided were:

a) Study NCT 00694798 (USFDA): "Study of Mycobacterium it, in BCG Refractory Superficial Transitional Cell Carcinoma of Bladder (STCC)."

The protocol admits patients who have failed to achieve disease-free state at six months after initiation of therapy or patients who have recurrence of tumor within three months after completion of treatment or adequate retreatment, but excluding patients with certain co morbidity conditions, including i.e., immuno-compromised.

The investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of my information and belief, in using the present invention, the health regulatory authorities who approved the trials had no difficulty, to the best of my information and belief, in understanding how to use the invention.

b) Study NCT00525408 (US FDA) : "A Study of Mycobacterium w Plus Docetaxel for Hormone Refractory Metastatic Prostate Cancer (HRPC)"

The protocol admits patients with prostate cancer who have become refractory to hormone therapy and also has developed metastasis. This is a controlled trial wherein efficacy of *Mycobacterium w* plus Docetaxel is compared with Docetaxel alone (Standard of Care).

The investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of my information and belief, in using the present invention. The health regulatory authorities who approved the trials had no difficulty, to the best of my information and belief, in understanding how to use the invention.

c) Study NCT00694915 (US FDA) : "Study of Mycobacterium w in Superficial Transitional Cell Carcinoma of Bladder (STCC)"

The protocol admits patients with newly diagnosed superficial transitional cell carcinoma with completely resected papillary tumors and high probability of recurrence risk i.e. stage T1 Grade 2, T1 Grade 3 & CIS. This is a controlled study to compare efficacy of *Mycobacterium w* intradermal to intravesical BCG (Standard of care) in patients with superficial bladder cancer.

The investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of my information and belief, in using the present invention. The health regulatory authorities who approved the trials had no difficulty, to the best of my information and belief, in understanding how to use the invention.

c) Study NCT00680940 (US FDA): A Study of Mycobacterium w in Combination with Paclitaxel Plus Cisplatin in Advanced Non Small Cell Lung Cancer (NSCLC)

The protocol admits patients with advanced small cell lung cancer. This is a controlled study to compare efficacy of *Mycobacterium w* in combination with Paclitaxel plus Cisplatin in advanced non small cell lung cancer to that of Paclitaxel plus Cisplatin (Standard of Care).

To the best information and belief of the inventor, in none of these trials, the investigators, the health regulatory authorities who approved the trials, have had any difficulty in carrying out the teachings of the present invention. It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation.

Action refers to the examples provided in the specification as "anecdotal." The term "anecdotal" in Merriam Webster dictionary is defined as "[c]onsisting of reports or observations of usually unscientific observers." With evidence of various types of cancer which could be treated by following the teachings of the present invention and with the knowledge available to one of skill in the art (discussed in greater detail on pages 14 and 15 of this response), and with the evidence of clinical trial having been approved by regulatory authorities, such as FDA, as shown above, Applicant respectfully requests the Office to explain *why* it doubts the truth or accuracy of any statement in the supporting disclosure. "[i]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." ***In re Marzocchi***, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

It is respectfully submitted that the reliance in the Action on *Genentech, Inc. v. Novo Nordisk* 935 F. Supp. 260 (S.D.N.Y. 1996) to support its assertion that enablement criteria can only be satisfied by providing "[a]ctual composition administered to the patients . . . ." is legally flawed because in *Genentech* at issue was the use of cleavable fusion expression to make human growth hormone (hGH) when the specification "[d]id not describe in any detail whatsoever how to make hGH using cleavable fusion expression". At the time of Genentech's filing, trypsin and other like enzymes were used only to digest proteins, not to specifically and precisely cleave conjugate proteins to yield intact, useful proteins and that prior art explicitly indicated that

trypsin would not be useful for the cleavable fusion expression of arginine-containing proteins such as hGH.

There is no mention in *Genentech* for a need to provide dosage amounts or product to be used or the frequency of administration to support enablement. Therefore, no correlation exists between *Genentech* and this study.

The applicable law is that "[A] claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *Falkner v. Inglis*, 448 F.3d 1357, 1366 USPQ2d 1001 (Fed. Cir. 2006) (quoting *LizardTech*, 424 F. 3d 1336 , 1345 (Fed. Cir. 2005).

In POSITION 4, the Action asserts "[C]ancer treatment is an extremely unpredictable art with a solid statistical data required to support it." Applicant respectfully traverses because it is explicitly stated in MPEP that "[a]pplicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted." MPEP 2107.03.

In the instant application, Applicant provides examples of various types of cancer which could be treated by following the teachings of the present invention and with the knowledge available to one of skill in the art. For example, the specification discloses:

1. A 70 year old female suffering from multiple myeloma . . . was given [pharmaceutical composition as per present invention] intradermally over deltoid region at the interval of one week. At the end of 3 months [her] condition [] improved drastically . . . . Her hemoglobin value has risen to 7.7 gm/dl from 5.5 gm/dl. Paragraph 87.

2. A 50 year old postmenopausal woman underwent lumpectomy for a fumigating mass in her [] breast (carcinoma breast). Following surgery she developed cough and breathlessness . . . due to large metastatic lesion in her chest. A pharmaceutical composition as per present invention was added to her therapy. At the end of the three months, there was a remarkable improvement in her cough and breathlessness. X-ray chest showed 25% decrease in size of metastatic lesion. Paragraph [0087].

3. A 68 year old male suffering from carcinoma esophagus-midthird . . . [was subjected to therapy] with a pharmaceutical composition [per present invention] . . . It resulted in improvement in his symptoms gradually. . . . The pharmaceutical composition as per present invention was given as 0.1 ml intradermally at weekly interval 2nd dose was delayed and administered at the interval of 15 days instead of 1 week. It comprised of 0.3 ml instead of 0.1 ml. Paragraph [0089].

4. In four patients with superficial bladder cancer . . . pharmaceutical composition as per present invention was given intradermally. It was given as 0.1 ml every month. By six weeks (after two injections) [patients] became asymptomatic. Paragraph [0093].

5. Five patients with muscle invasive bladder cancer were treated by intradermal injection of *Mycobacterium w* over both deltoid. The intradermal *Mycobacterium w* was repeated every month on any on deltoid for six months . . . At the end of two months all [patients] were symptom free. Paragraphs [0097-98].

6. In a controlled study involving 20 patients with a breast cancer and bone metastasis effect of *mycobacterium w* was evaluated . . . *Mycobacterium w* containing compositions were given as intradermal injections of 0.1 ml every week for two months followed by every 15 days for two months and monthly for two months for a total duration six months. 10 patients of 20 randomly received it while remaining 10 were kept as controls. None of the patients in treatment group developed diarrhea and vomiting compared to 8 of 10 patients in control group. Paragraphs [0105-0106].

7. In a controlled study in 20 patients with histologically proven advanced head and neck cancer with minimum of 6 months expectancy effect of *mycobacterium w* was evaluated.

Each patient received chemotherapy containing cisplatin and 5-FU. *Mycobacterium w* was given to randomly selected 10 patients as 0.1 ml intradermally over deltoid region every 15 days for 3 months. The first dose was given as 0.2 ml divided over two deltoid region . . . Nausea/vomiting was seen in all patients in control group while in none in treatment group. Thus use of *mycobacterium w* was useful in reducing side effects of chemotherapy. Paragraphs [0108-0112].

8. A 65 year old male patient was diagnosed to have carcinoma pancreas with metastasis in liver and lung . . . He was administered *Mycobacterium w* 0.3 ml intradermally biweekly. Within 10 day his cough was controlled and general condition showed improvement. Paragraph [0113].

With these disclosures in the application, Applicant has met the statutory requirement of objective enablement. "[N]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). As set forth in *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

For the above reasons Applicant submit that the claims are enabled.

CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such action is hereby solicited.

A telephonic interview between the Examiner and Applicant's representative below is requested to resolve any remaining issues and answer any questions the Examiner may have. Please call the undersigned attorney at 617-345-3691 to conduct the substantive interview or briefly to arrange a time for it (or arrange by e-mail to shasan@burnslev.com).

Respectfully submitted,

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APPENDIX B

Cancer pain relief

SECOND EDITION

With a guide to
opioid availability

World Health Organization
Geneva
1996

WHO Library Cataloguing in Publication Data

Cancer pain relief : with a guide to opioid availability
— 2nd ed.

1. Neoplasms – drug therapy 2. Pain – drug therapy
3 Palliative treatment 4. Narcotherapy

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Contents

large doses of naloxone, up to 4 mg, may be necessary to reverse respiratory depression caused by buprenorphine.

Rare effects. Occasionally, a patient may experience opioid-induced psychotic symptoms or symptoms relating to histamine release (pruritus, bronchoconstriction). These patients should be changed to an alternative strong opioid analgesic (see Table 4).

Alternative routes for administration of morphine and other opioids

Most patients are able to take morphine and other opioids by mouth. Towards the end of life, however, it is often necessary to make use of alternative routes because of dysphagia.

Rectal administration

Morphine may be given per rectum; this is as effective as by mouth. It is contraindicated in immunosuppressed neutropenic patients because minor rectal trauma may result in local cellulitis.

In some countries, morphine suppositories are available in strengths ranging from 10 mg to 60 mg. When suppositories are not available, morphine can be given by rectal enema, in 10–20 ml of water. Slow-release tablets can also be given by this route. Other opioids can also be given per rectum. This route should not be used in patients with diarrhoea or faecal incontinence.

Subcutaneous administration

In patients unable to take oral or rectal morphine, the subcutaneous route should be used. Repeated injections should be avoided if possible because most patients find them unpleasant. Continuous subcutaneous infusion using a portable syringe driver is preferable. If a syringe driver is not available, a butterfly cannula can be left *in situ* and morphine injected intermittently. By injection, most patients need one-third to one-half of the previously satisfactory oral dose. Buprenorphine, hydromorphone and levorphanol can also be given subcutaneously.

Intramuscular administration

If given by injection, pethidine should be given intramuscularly because it causes tissue irritation.

Intravenous administration
Opioids may be given intravenously by either bolus injection or continuous infusion.

> The dose of morphine or other opioid is the same whether given subcutaneously, intramuscularly or intravenously.

Spinal administration
The epidural and intrathecal routes provide pain relief with few adverse effects. These routes are important in patients who experience severe adverse effects or who have pain that is poorly responsive to opioids. As spinal administration requires special expertise and equipment for catheter placement, these routes will not be practicable in many settings.

If a patient has developed physical dependence on opioids administered by more conventional routes, withdrawal symptoms may occur when spinal administration is started. These may be avoided by continuing to give one-quarter of the dose by the former route, reducing the amount progressively over several days.

Transdermal administration
Certain drugs, with an adequate oil/water partition coefficient, low relative molecular mass and sufficient potency, can be administered transdermally. Fentanyl citrate has recently been proposed for administration by this route. Application of fentanyl patches produces a slow increase in plasma levels of the drug: peak plasma concentrations are achieved after 12–24 hours and a depot remains in the skin for 24 hours after the patch is removed. Rescue medication may be necessary during the first 24 hours. Doses vary from 75 µg/hour to 350 µg/hour. Compliance of patients is generally very good, but the cost of this method and its current limited availability restrict its use.

Drugs for neuropathic pain

As with nociceptive pain, drug treatment is the mainstay of man-

must be legally responsible for safe storage and the recording of opioids received and dispensed.

Reasonable record-keeping and accountability provisions should not discourage health care workers from prescribing or stocking adequate supplies of opioids.

3. *Prescriptions.* A prescription for opioids should contain at least the following information:
   - name and address of the patient,
   - date of issue,
   - drug name, dosage strength and form, quantity prescribed,
   - directions for use,
   - physician's name and business address,
   - physician's signature.
4. *Patient access.* Opioids should be available in locations that will be accessible to as many cancer patients as possible.
5. *Medical decisions.* Decisions concerning the type of drug to be used, the amount of the prescription and the duration of therapy are best made by medical professionals on the basis of the individual needs of each patient, and not by regulation.
6. *Dependence.* Physical dependence, which may develop when opioids are used to treat chronic pain, should not be confused with psychological dependence.